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EXAMINER	
JOHANNSEN, DIANA B	
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1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,360	KERB ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-35* is/are rejected.

7)☒ Claim(s) *35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0205*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application has been transferred from Ex. J. Sitton to Ex. D. Johannsen. The application remains assigned to Art Unit 1634.

2. This action is responsive to the Response including a complying complete set of claims filed on July 28, 2008. Claims 29-31 and 34-35 have been amended and claims 1-28, 36-37, and 41 have been canceled. Claims 29-35 are now pending and under consideration.

3. This application is a 371 of PCT/EP03/09356, filed August 22, 2003. It is noted that the international search report for PCT/EP03/09356 has been received and considered.

Election/Restrictions

4. Applicant's election of Group VIII, claims 29-35, and of SEQ ID NOS 4 and 28, in the reply filed on March 17, 2008 (reiterated in the reply of July 28, 2008) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

5. All claims now pending (claims 29-35) are drawn to the elected invention.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

a) Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

b) The oath/declaration includes an improper priority claim to a foreign application under 35 USC 119(e) (which pertains to US provisional applications); the foreign priority claim should be made under 35 USC 119(a)-(d).

c) The oath/declaration includes an improper priority claim under 35 USC 120 to the same PCT application of which the instant application is a 371.

Priority

7. Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on a European application filed on August 23, 2002. Applicant's priority claim is considered valid because the European application is referenced in applicant's oath/declaration and because the priority claim was already granted in the PCT application of which the instant application is a 371; however, applicant is reminded that the new oath/declaration required above should list the European application in the proper location.

Information Disclosure Statement

8. Regarding the IDS filed February 23, 2005, it is noted that the examiner has completed many of applicant's citations so as to allow for consideration of the cited references. Applicant is requested to review and acknowledge the corrections, or, if necessary, provide a substitute 1449 for consideration.

Specification

9. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material

incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

In the present case, GenBank Accession Numbers GI: 9581607 and GI: 2511670 are recited in applicants' claims, such that the actual sequence information associated with the Accession Numbers is required to practice the claimed methods and is therefore essential material. It is noted that the instant Accession numbers were present in applicants' originally filed claims, and that the inclusion therein is considered to constitute clear intent to incorporate by reference the material associated with the Accession numbers. However, as incorporation by reference to a source such as a GenBank entry of such essential material is improper, the actual sequence information must be added to the application.

10. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. (For example, none of the claims under consideration are directed to therapeutic applications.)

11. The disclosure is objected to because of the following informalities: the specification lacks a separate "Brief Description of the Drawings". This objection may be overcome by amending the specification to insert the required heading at the top of page 44. Appropriate correction is required.

12. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code (see, e.g., page 16). See MPEP § 608.01.

13. The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a) and (a)(2). However, the specification fails to comply with one or more of the requirements of 37 CFR 1.821 through 1.825 because the specification recites sequences that lack description by the appropriate sequence identifier set forth in the "Sequence Listing" as required by 37 CFR 1.821(d). See, for example, page 47. Appropriate corrections for compliance are required.

Claim Objections

14. Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, claim 35 appears to require steps (a) and (b) of claim 34, rather than the method in its entirety. Thus, while claim 34 includes a requirement, e.g., for “detection of a polynucleotide” (see preamble of claim 34), claim 35 does not encompass this limitation, and therefore is not a proper dependent claim.

Claim Rejections - 35 USC § 112, second paragraph

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 29-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29-30 and 32-33 are indefinite because it is not clear whether the claims are drawn to a method of diagnosis, as set forth in the preamble of claim 29, or to a method of determining the presence of a polynucleotide in a sample, as indicated in the method step of the claims. The language of the claim does not make clear how (or even whether) the step of determining the presence of a polynucleotide actually relates to or results in the "diagnosing" of the preamble. Accordingly, clarification is required.

Claim 31 is indefinite because it is not clear whether the claims are drawn to a method of diagnosis, as set forth in the preamble of the, or to a method of determining the presence of a polypeptide in a sample, as indicated in the method step of the claim. The language of the claim does not make clear how (or even whether) the step of determining the presence of a polypeptide actually relates to or results in the "diagnosing" of the preamble. Accordingly, clarification is required.

Claims 30-31 are indefinite over the recitation of the limitation "polypeptide or fragment therefore" in each of the claims, because it is not clear how a fragment "therefore" might relate to the polypeptide. Further, there is insufficient antecedent basis in each of the claims for the limitation "said polypeptide or fragment thereof,"

because the claims do not previously refer to such a fragment. Each of these rejections could be overcome by amending the claims to recite "fragment thereof" in lieu of "fragment therefore."

Claims 29-35 are indefinite over the recitation of the limitation "said polynucleotide has at least one nucleotide exchange or deletion at position 109130 of the OCT1 gene (GenBank Accession No: GI:9581607)" in claims 29-31 and 34, item (c). First, it is not clear how the recitation of "(GenBank Accession No: GI:9581607)" actually limits the claims; for example, it is not clear what material associated with the Accession No. is actually required, and further as to how much weight is to be given to the material recited within parentheses as compared to the remainder of the claim. Additionally, as the claims as written do not actually require a sequence having a "position 109130," it is not clear how one would determine whether a particular polynucleotide is or is not encompassed by the claims. For example, how is "position 109130" to be identified in the polynucleotide, and further, how one would conclude or determine that a particular polynucleotide includes an "exchange or deletion" at this position? Accordingly, the language of the claims does not clearly apprise one of skill in the art as to what polynucleotides are actually encompassed thereby.

Claims 29-35 are indefinite over the recitation of the limitation "said polynucleotide has at least one nucleotide substitution at a position corresponding to position 109130 of the OCT1 gene (GenBank Accession No: GI:9581607)" in claims 29-31 and 34, item (d). First, it is not clear how the recitation of "(GenBank Accession No: GI:9581607)" actually limits the claims; for example, it is not clear what material

associated with the Accession No. is actually required, and further as to how much weight is to be given to the material recited within parentheses as compared to the remainder of the claim. Additionally, as the claims as written do not actually require a sequence having a "position 109130," and as the specification includes no clear definition of the language "corresponding to," it is not clear how one would determine whether a particular polynucleotide is or is not encompassed by the claims. For example, how is a "position corresponding to position 109130" to be identified in the polynucleotide, and further, how one would conclude or determine that a particular polynucleotide includes a substitution at this position? Accordingly, the language of the claims does not clearly apprise one of skill in the art as to what polynucleotides are actually encompassed thereby.

Claims 29-35 are indefinite over the recitation of the limitation "said polynucleotide has a T at a position corresponding to position 109130 of the OCT1 gene (GenBank Accession No: GI:9581607)" in claims 29- 31 and 34, item (e). First, it is not clear how the recitation of "(GenBank Accession No: GI:9581607)" actually limits the claims; for example, it is not clear what material associated with the Accession No. is actually required, and further as to how much weight is to be given to the material recited within parentheses as compared to the remainder of the claim. Additionally, as the claims as written do not actually require a sequence having a "position 109130," and as the specification includes no clear definition of the language "corresponding to," it is not clear how one would determine whether a particular polynucleotide is or is not encompassed by the claims. For example, how is a "position corresponding to position

109130" to be identified in the polynucleotide, and further, how one would conclude or determine that a particular polynucleotide includes a T at this position? Accordingly, the language of the claims does not clearly apprise one of skill in the art as to what polynucleotides are actually encompassed thereby.

Claims 29-35 are indefinite over the recitation of the limitation "said polypeptide comprises an amino acid substitution at position 61 of the OCT1 polypeptide (GenBank Accession No: GI:2511670)" in claims 29-31 and 34, item (f). First, it is not clear how the recitation of "(GenBank Accession No: GI:2511670)" actually limits the claims; for example, it is not clear what material associated with the Accession No. is actually required, and further as to how much weight is to be given to the material recited within parentheses as compared to the remainder of the claim. Additionally, as the claims as written do not actually require a sequence having a "position 61," it is not clear how one would determine whether a particular polypeptide is or is not encompassed by the claims. For example, how is "position 61" to be identified in the polypeptide, and further, how one would conclude or determine that a particular polypeptide includes a substitution at this position? Accordingly, the language of the claims does not clearly apprise one of skill in the art as to what polypeptides are actually encompassed thereby.

Claims 29-35 are indefinite over the recitation of the limitation "said polypeptide comprises an amino acid substitution of R to C at position 61 of the OCT1 polypeptide (GenBank Accession No: GI:2511670)" in claims 29-31 and 34, item (g). First, it is not clear how the recitation of "(GenBank Accession No: GI:2511670)" actually limits the claims; for example, it is not clear what material associated with the Accession No. is

actually required, and further as to how much weight is to be given to the material recited within parentheses as compared to the remainder of the claim. Additionally, as the claims as written do not actually require a sequence having a "position 61," it is not clear how one would determine whether a particular polypeptide is or is not encompassed by the claims. For example, how is "position 61" to be identified in the polypeptide, and further, how one would conclude or determine that a particular polypeptide includes a "substitution of R to C" at this position? Accordingly, the language of the claims does not clearly apprise one of skill in the art as to what polypeptides are actually encompassed thereby.

Claim 33 is indefinite because it is not clear how the claim further limits claim 29, from which it depends. With regard to the recitations "fluorescent dye and quenching agent-based PCR assay (Taqman PCR detection system)", "extension based assays (ARMS, (Amplification Refractory Mutation System)", and "solid phase hybridization (dot blot, reverse dot blot, chips)", it is not clear how, or even whether, the material contained with parentheses actually limits the claim. With regard to the recitations "single strand conformational polymorphism (SSCP)" and "microarrays," it is not clear how these entities relate to the method being claimed; if these recitations were intended to require the use of SSCP analysis, or of a method step employing microarrays, the claim should be amended so as to make this clear. With regard to the recitation "invader (Third wave technologies)," it is similarly unclear how the recitation "invader" (as opposed to, e.g., an "invader assay") limits the claims; further, the manner in which "(Third wave technologies)" limits the claims is also unclear (for example, is this

recitation intended to require that materials be obtained from a particular source?). Accordingly, clarification as to the manner in which claim 33 further limits claim 29 is required.

Claims 34-35 are indefinite over the recitation "said polynucleotides" in the second and third lines of step (a) of claim 34. While the claim previously refers to various individual polynucleotides in the alternative, there is no previous recitation of any group of polynucleotides that might constitute "said polynucleotides." Therefore, clarification is required with regard to what group of molecules is referenced by this term.

Claims 34-35 are indefinite over the recitation of the phrase "which is assembled on an optical filter substrate with the sample under conditions allowing interaction of said polynucleotide with the immobilized targets on the solid support" in step (a) of claim 34. First, as the claim does not previously refer to any "immobilized targets," there is insufficient antecedent basis for this terminology in the claim. Second, it is not clear how this phrase in its entirety limits the claims. For example, what is "assembled on an optical filter substrate" (e.g., does this refer to only the previously recited "bead array," to the bead array and the sample, to any of the previously recited solid supports with the sample, or without the sample, etc.). Further clarification is required with regard to how this phrase limits the claimed method so as to clearly apprise one of skill in the art as to what would and would not infringe the claimed invention.

Claims 34-35 are indefinite because it is not clear how the method steps of the claim allow one to determine "prevalence for said disease" as set forth in claim 35. (It is

noted that this rejection pertains to independent claim 34 to the extent that it encompasses the method of claim 35.) Particularly, the language of the claim does not make clear how binding of "said polynucleotide" relates to disease prevalence. Further, the preamble of the claim requires "diagnosing," and it is unclear how or whether determining prevalence relates to "diagnosing." Accordingly, clarification is required.

Claim Rejections - 35 USC § 112, first paragraph

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 29-35 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The sequence information associated with GenBank Accession Nos. GI:9581607 and GI:2511670 that is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The practice of the invention claimed requires polynucleotides defined by reference to the sequences associated with these Accession Nos. and particular positions therein; thus, knowledge of these sequences is essential to the practice of the invention. Accordingly, the sequences themselves constitute critical or essential material that cannot properly be incorporated by reference (as discussed above), and applicants' failure to actually recite the sequences (by, e.g., their inclusion in the Sequence Listing and reference in the claims to corresponding SEQ ID NOs) renders the claims non-enabled.

19. Claims 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 29-30 and 32-33 are drawn to methods of "diagnosing a disorder related to the presence of a molecular variant of an OCT1 gene or susceptibility to such a disorder" in which the presence of a polynucleotide selected from (a)-(g) as set forth in claim 29 is determined in a sample from a subject; claim 30 further comprises determining the presence of an encoded polypeptide or an antibody that binds specifically thereto. Claim 31 is drawn to a method of "diagnosing a disorder related to the presence of a molecular variant of an OCT1 gene or susceptibility to such a disorder" in which the presence of a polypeptide selected from (a)-(g) as set forth in

claim 31, or an antibody that binds specifically thereto, is determined in a sample from a subject. Claims 34-35 are drawn to a method of detection of a polynucleotide comprising a polynucleotide selected from (a)-(g) of claim 34 in which the binding of a polynucleotide to targets immobilized on a solid support is determined; claim 35 further requires that the steps of claim 34 be employed "for diagnosing a disease" wherein binding "is indicative for the presence or the absence of said disease or a prevalence for said disease."

Regarding claims 29-33, it is again noted that applicants' claim language does not make clear how the method steps recited in the claims relate to the uses of "diagnosing a disorder related to the presence of a molecular variant of an OCT1 gene or susceptibility to such a disorder" (claims 29-33). As applicants' claims recite a use of "diagnosing a disorder related to the presence of a molecular variant of an OCT1 gene or susceptibility to such a disorder," enablement of the claims must be evaluated with respect to this asserted use. Claim 35 is drawn to a method of "diagnosing a disease" wherein binding of the polynucleotide of the claims "is indicative for the presence of the absence of said disease or prevalence for said disease." Claim 34, from which claim 35 depends, also encompasses the methods of claim 35.

Further, while claims 29-34 broadly encompass detection of fragments of polynucleotides/polypeptides that are identical to wild-type sequences (note, e.g., the text of claims 29-31 and 34, (f) and (g)), as indicated in the rejection under 35 USC 102(b), below, the claims are primarily directed to the use of polynucleotides including variations at the nucleotide position encoding amino acid 61 of the OCT1 gene, or to

polypeptides encompassing a substitution at this position. This rejection applies to the claims to the extent that they are drawn to methods employing such variant polynucleotides and polypeptides.

The specification teaches that these variant polynucleotides/polypeptides are useful in methods of diagnosing diseases, particularly diseases associated with drug responses and side effects (see pages 13-14); accordingly, use of these variant molecules in the diagnosis of such diseases/disorders, as set forth in the specification and also in the claims, constitutes applicant's asserted utility. MPEP 2164.07 discusses the need for applicant's asserted utility to be enabled by the specification:

> The requirement of 35 U.S.C. 101 is that some specific, substantial, and credible use be set forth for the invention. On the other hand, 35 U.S.C. 112, first paragraph requires an indication of how the use (required by 35 U.S.C. 101) can be carried out, i.e., how the invention can be used. If an applicant has disclosed a specific and substantial utility for an invention and provided a credible basis supporting that utility, that fact alone does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph. For example, if an applicant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard, but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. 112, but not 35 U.S.C. 101.

In the instant case, applicant's claims meet the requirements of 35 USC 101, as applicant has provided a credible basis supporting the utility of using variant OCT1 polynucleotides and polypeptides in diagnosing diseases associated with drug responses and side effects (see discussion below); however, enablement is lacking with regard to the actual practice of the methods of the instant claims.

It is unpredictable as to whether one skilled in the relevant art could actually use applicant's claimed invention. The specification exemplifies the screening of the human OCT1 gene in a population of "Caucasian individuals," and discloses a variety of newly

identified and prior art variations in the human OCT1 gene, as well as amino acid changes corresponding to a subset of those variations (see, e.g., Example 1 at pages 45-49, and the summary of variations at pages 42-43). The specification exemplifies the characterization of 5 human OCT1 gene variants, including the Arg61Cys variant encompassed by the present claims, by evaluation of the uptake of various substrates in Xenopus laevis oocytes expressing the variants (Example 2); applicants report that the uptake of the substrate MPP is reduced 70% (as compared to wild-type) in the Arg61Cys variant, and reduced by more than 98% in the Cys88Arg and Gly401Ser variants, with no significant difference being measured for the Phe160Leu and Met420del variants (see top of page 51). Significant changes in substrate specificity were detected with the Cys88Arg and Gly401Ser mutants but not with the other 3 mutants (top of page 51). In Example 3, when applicants assayed for correlations between variants and drug-induced cholestasis and hepatic side effects in human patients, only Met408Val and the linked 8 bp deletion were reported to be associated with cholestasis, and only the Gly401Ser variant was associated with hepatic side effects (page 52-53). No data regarding any significant associations between the elected Arg61Cys variant and any disease or condition in patients is reported in the specification. Further, applicants' data indicates that findings in the Xenopus oocyte assays are not clearly predictive of any disease or condition in patients; for example, of the variants assayed by applicants, only the Gly401Ser variant appears to have exhibited both impaired uptake in the oocyte assay and a significant disease association (i.e., the association with hepatic side effects). Based on the teachings of the

specification, one of skill in the art would recognize that applicants do have a credible basis for asserting that polynucleotides encoding, and polypeptides including, the elected Arg61Cys variant may be associated with a disease or disorder in patients; however, applicants have yet to actually establish the existence of such an association, or establish what types of disease or disorders this variant is actually associated with (if any). Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance with regard to the enablement of a claimed invention. In the instant case, Kerb et al (Pharmacogenetics 12:591-595 [Nov 2002]; cited in the IDS of 2/2005) report what appears to be some of the same data reported in the specification (see entire reference, particularly Figure 1), and conclude with regard to the Cys88Arg and Gly401Ser mutants that "Since two mutations have dramatic effects on transport of OCT1 substrates *in vitro* it is quite likely that these mutations will also affect the *in vivo* disposition of OCT1 substrates" (page 594, right column). Thus, Kerb et al suggest that the Cys88Arg and Gly401Ser mutants are "likely" to have *in vivo* effects, but do not draw the same conclusion regarding the Arg61Cys variant. Further, the prior art reference Shu et al (Clinical Pharmacology & Therapeutics 71(2):P73 [Feb 2002]; cited in the IDS of 2/2005) discloses that a human OCT1 variant identified as 'Variant 3" was found to be non-functional in the oocyte assay, and suggest performing "clinical evaluation of drug response in individuals who carry Variant 3;" however, the teachings of Shu et al suggest that further testing is necessary to determine whether a variant that is "non-functional" *in vitro* actually exhibits a phenotype *in vivo*. Thus, the teachings of the specification and of the art suggest that further experimentation and

testing are needed to determine whether the Arg61Cys variant is in fact associated with any type of disease or disorder. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to perform such further testing; however, the outcome of such experimentation is completely unpredictable. As it is unknown whether any quantity of experimentation (even an infinite amount) will actually result in the identification of any type of disease association, the quantity and type of experimentation required to enable the claimed invention is clearly undue. It is further noted that the claims encompass methods practiced in any type of "subject," and that the teachings of the specification and of the art have not established enablement of the claimed invention in humans or any other type of subject that possesses an OCT1 gene. Additionally, the claims are not limited to, e.g., particular molecules that where assayed by applicants (e.g., molecules that constitute OCT1 genes or proteins having a single substitution relative to wild type human OCT1), but rather broadly encompass thousands of different molecules that are merely 70% identical to an OCT1 gene, or that are "capable of hybridizing," thereto, etc. As enablement has not been established even with regard to a single particular variant molecule, enablement is also lacking with regard to this large genus of related molecules. Finally, it is noted that the specification and the prior art are also silent with regard to identification or detection of any antibody that "binds specifically" to any Arg61Cys OCT1 variant, either in association with disease or otherwise; accordingly, it would also require undue experimentation to use this embodiment of applicants' claimed invention.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 29-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (Molecular Pharmacology 51:913-921 [1997]).

It is noted that the claims broadly encompass detection of fragments of polynucleotides/polypeptides and that the claims do not require that the fragments detected actually include or encode a substitution; i.e., the claims broadly encompass the detection of fragments that are identical to wild-type sequences (note, e.g., the text of claims 29-31 and 34, (f) and (g)).

Zhang et al disclose determining the presence of a polynucleotide comprising a polynucleotide that encodes a fragment of an OCT1 polypeptide, as set forth in (f) and (g) of claims 29 and 34 (see entire reference, particularly the procedures at pages 914, noting the isolation, amplification and sequencing of hOCT1 from human liver at page 914, and the Northern analysis of human tissues at page 915). Zhang et al therefore teach methods comprising all of the steps required by claims 29 and 32-33; it is noted that dependent claim 33 recites, e.g., sequencing, "PCR based assays", and solid phase hybridization. With further regard to claims 30-31, Zhang et al also disclose determining the presence of a polypeptide encoded by a polynucleotide comprising a polynucleotide encoding a fragment of an OCT1 polypeptide, as set forth in (f) and (g)

(see, e.g., the protein detection disclosed at page 915, left column). Thus, Zhang et al teach methods including all the steps required by claims 30-31. With further regard to claim 34, the Northern analysis disclosed by Zhang et al requires contacting a solid support (the blot itself) comprising one or more immobilized polynucleotides with a polynucleotide meeting the requirements of the claims, as noted above, wherein binding of said polynucleotide to said immobilized polynucleotides is determined. Accordingly, Zhang et al also teach methods comprising all steps required by claim 34. With regard to the recitation in the preambles of claims 29 and 31 of the intended use of "diagnosing a disorder related to the presence of a molecular variant of an OCT1 gene or susceptibility to such a disorder" it is noted that MPEP 2111.02 states that:

> If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999).

Further, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, the claims merely require step(s) of determining the presence of a polynucleotide/polypeptide in a sample and include no actual method steps that relate to the recited intended use; in other words, there is no

manipulative difference between applicants' claimed methods and those of Zhang et al, such that the recitation "of diagnosing....." is considered to constitute an intended use that is non-limiting for purposes of comparing the claimed invention to the prior art. It is also noted that claim 32 recites a further limitation on the intended use without requiring any further limitation of the actual method steps of the claimed invention. Thus, Zhang et al anticipate claims 29-34. (It is noted that claim 35 was excluded from the present rejection because the claim clearly requires a nexus between binding and diagnosis).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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